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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Chun-Ming Chen, Charles Carpenter, Haoyi Gu, Au Naqui

Serial No.: 08/942,369

Filed: October 2, 1997

For: METHOD AND APPARATUS FOR CONCURRENTLY DETECTING PATHOGENIC ORGANISMS AND ANTIMICROBIAL SUSCEPTIBILITY

Group Art Unit: 1623
Examiner: M. Moran

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Sir:

Transmitted herewith is an Appeal Brief, in triplicate, for the above-identified application.

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APPELLANT'S BRIEF ON APPEAL
SUBMITTED PURSUANT TO 37 C.F.R. § 1.192

Mail Stop Appeal Brief-Patents
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant hereby appeals the Examiner's final rejection mailed January 3, 2003 and pursuant to the Notice of Appeal filed April 2, 2003 hereby submits this Appeal Brief under 37 C.F.R. § 1.192. This brief is timely filed on or before June 7, 2003. Because an Appeal Brief was previously filed in this case and the Examiner placed the case back into prosecution after further searching, no fee is due with this Appeal Brief. MPEP 1208.02.

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REAL PARTY IN INTEREST

IDEXX Laboratories, Inc. is the sole assignee of the above captioned patent application.

RELATED APPEALS AND INTERFERENCES

The Applicants are not aware of any pending matters before the Board of Patent Appeals and Interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF THE CLAIMS

Claims 20-24, 26, and 31-43 are pending in the above captioned application. All other claims have been previously cancelled.

Claims 20-24 and 31 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of Johnson in view of Libman and Thaller. (Advisory Action mailed 1/3/03).

Claims 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson in view of Libman and Thaller, and further in view of Odaka (Advisory Action mailed 1/3/03).

Claims 26 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson in view of Libman and Thaller, and further in view of Brocco (Advisory Action mailed 1/3/03).

Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Johnson in view of Libman, Thaller, and Odaka, and further in view of Brocco (Advisory Action mailed 1/3/03).

All pending claims (claims 20-24, 26 and 31-43) are the subject of this appeal.

STATUS OF AMENDMENTS

No amendments have been filed subsequent to final rejection.

SUMMARY OF THE INVENTION

Bacterial-urinary tract infections are one of the most common veterinary diseases, and also occur in humans. The primary causative agents of urinary tract infections are the primary Gram-negative urinary pathogens. This group of organisms includes *E. coli*, *Klebsiella spp.*, *Enterobacter spp.*, *Proteus mirabilis*, *Proteus vulgaris*, *Morganella morganii*, *Providencia reterri*, *Acinetobacter spp.* and *Enterococcus faecalis*. (specification, p. 8, lines 22-26). Although the great majority of urinary tract infections (UTI) are caused by a single type of organism in any particular case, contaminating flora are normally present on a patient's skin or fur, or in the environment. In the veterinary context, collection of a urine specimen for analysis may often result in the specimen running along the patient's skin or fur and being contaminated by bacteria, or otherwise being collected in a non-sterile manner.

The present application claims methods of detecting the presence or absence of urinary pathogens in a biological sample and of simultaneously determining the susceptibility of the pathogens to various antimicrobial agents (p. 7, line 21 - p. 8, line 26). The present invention accomplishes this in part by providing a uropathogen specific medium, which is a medium that allows only the growth of the primary urinary Gram-negative pathogens and allows for substantially less growth of any other bacteria of a biological matrix (specification p. 12, line 11 et seq.; p. 19, Table 1). The specification defines the primary Gram-negative urinary pathogens as the group of bacteria which cause at least 85-90% of the human and veterinary urinary tract infections (specification, p. 10, line 19 et seq.). These terms define the claimed subject matter.

The methods of the invention involve the use of a multicompartment assay device having at least three compartments. A first compartment contains a medium capable of sustaining the growth of total microbial organisms (i.e., a positive control); a second compartment contains a uropathogen specific medium (which allows for the growth only of the primary urinary Gram-negative pathogens); and one or more additional compartments containing an antimicrobial susceptibility interpretation medium, which is a uropathogen specific medium containing an antimicrobial substance to be evaluated for its effect on any urinary pathogens present (p. 7, line 21-p.8, line 26).

The uropathogenic specific medium provided in the present invention is specific for primary Gram-negative urinary pathogens. The primary Gram-negative urinary pathogens are defined in the specification as those bacteria which cause at least 85-90% of the human and veterinary urinary tract infections (p. 10, line 19 of specification). This group of organisms includes *E. coli*, *Klebsiella spp.*, *Enterobacter spp.*, *Proteus mirabilis*, *Proteus vulgaris*, *Morganella morganii*, *Providencia reterri*, *Acinetobacter spp.*, and *Enterococcus faecalis* (specification, p. 8, lines 22-26). The claimed invention enables the user to collect a nonsterile sample of urine, place it into the respective wells containing the total growth medium, the uropathogenic specific medium, and the media containing the antimicrobial agents to be tested, and incubate the samples to determine 1) whether any primary Gram-negative urinary pathogens are present, and if so, 2) which antimicrobial agents they are susceptible to.

Since media selective for the primary Gram-negative urinary pathogens are used, contaminated, non-sterile samples can be placed into the media and growth is nevertheless seen only if there is present a primary Gram-negative urinary pathogen. Thus, even in cases where a urine sample must be collected off of the floor of a veterinary examination room (which is

common in the veterinary context) or is otherwise contaminated, a correct determination of the presence and susceptibility of any primary Gram-negative uropathogens present can be simultaneously performed.

ISSUES

Whether the Examiner can sustain a prima facie case of obviousness for claims 20-24 and 31 over Johnson in view of Libman and Thaller, when this art lacks an essential feature of the claimed invention, specifically a uropathogen specific medium, and where no motivation is provided by the art to make the combination of references.

Whether the Examiner can sustain a prima facie case of obviousness under 35 U.S.C. § 103 for claims 38-42 over Johnson in view of Libman and Thaller, and further in view of Odaka, where Odaka also fails to describe a uropathogen specific medium or principles for creating one, and where no motivation is provided by the art to make the combination.

Whether the Examiner can sustain a prima facie case of obviousness under 35 U.S.C. § 103 for claims 26 and 37 over Johnson in view of Libman, Thaller, and Odaka, and further in view of Brocco where Brocco also fails to disclose a uropathogen specific medium or principles for creating one, and where no motivation is provided by the art to make the combination.

Whether the Examiner can sustain a prima facie case of obviousness under 35 U.S.C. § 103 for claim 43 over Johnson in view of Libman, Thaller, and Odaka, and further in view of Brocco where neither reference discloses a uropathogen specific medium or principles for creating one, and where no motivation is provided by the art to make the combination.

GROUPING OF CLAIMS

The group of Claims 20-24, 26, 31, and the group of Claims 32-37 do not stand or fall together. Claims 32-37 further recite that the uropathogen specific medium contains methyl-umbelliferyl substrate. The Examiner cites the combination of Thaller, Libman, and Johnson, and states that Thaller discloses a methyl-umbelliferyl substrate. But no motivation is provided to combine Thaller with Libman and Johnson.

The group of Claims 20-24, 26, 31, and the group of Claims 38-43 do not stand or fall together. Claims 38-43 recite that the uropathogen specific medium contains yeast extract. The Examiner cites the combination of Johnson, Libman, Thaller, and Odaka, and states that Odaka discloses the use of yeast extract in media. But no motivation is provided to combine Odaka with Johnson, Libman, and Thaller.

ARGUMENT

1. The References Cited By The Examiner

Johnson discloses a device for performing serial dilutions to determine the susceptibility of microorganisms to antibiotics. The device contains multiple growth wells in which concentrations of suitable agents are predeposited, dried, and rehydrated with inoculum (Col. 2, lines 27-34). The figures of the Johnson reference provide illustrations of the device. **Johnson does not disclose any medium whatsoever, nor any principles for creating a uropathogen specific medium.** Johnson also does not disclose any methods for identifying organisms, nor disclose the use of his device that purpose. Johnson does not disclose any method for determining the presence of the primary Gram-negative uropathogens and the simultaneous determination of their antimicrobial susceptibility.

Libman discloses an apparatus for collecting body fluids, particularly for the collection of mid-stream urine (Libman, Col. 1, lines 66-68). Libman does not disclose any original media at all, but Libman does refer to the use of prior art media including MacConkey agar, CLED agar, and EMB agar (Col 3, line 64 – Col. 4, line 15) in the apparatus. While these media are for the isolation and presumptive identification of urinary pathogens, these media are not uropathogen specific media as defined in the application and recited in the claims, for reasons further explained below. Libman does not disclose any method for determining the presence of the primary Gram-negative uropathogens and the simultaneous determination of their antimicrobial susceptibility.

Thaller discloses a medium called "T-mod medium." Like MacConkey agar, CLED agar, and EMB agar, the disclosed T-mod medium is a medium for isolation and presumptive identification of *Enterobacteriaceae*, many of which may be responsible for urinary tract infections. Thaller does not disclose a uropathogen specific medium as defined in the application and recited in the claims, and does not disclose any principles for creating such a medium. Thaller also does not disclose any method for determining the presence of the primary Gram-negative uropathogens and the simultaneous determination of their antimicrobial susceptibility.

Brocco discloses methods for assaying for the inhibition of microorganism growth in the presence of an antibiotic. **Brocco does not disclose any selective media at all.** Brocco uses non-selective media in the methods described. Since the media used by Brocco have no selective power, it is necessary to use a sterile device and sterile medium that contains a particular antibiotic, and to inoculate it with pure cultures of pre-grown bacteria (Brocco, p. 4, lines 3-11). This is done for the purpose of evaluating the susceptibility of those bacteria to particular

antibiotics. If the medium or device is not sterile, contaminating bacteria will grow and give a false result because, unlike the present invention, the medium of Brocco are not selective and allow many types of bacteria to grow. The result can only be correlated to the bacteria tested if the medium was inoculated with a pure culture of that bacteria. In the present invention, these sterility concerns are unnecessary because the medium is selective for the primary Gram-negative urinary pathogens, i.e., only this class of bacteria will grow in the media.

Odaka discloses a culture medium for the multiplication of *Colibacillus*. Odaka does not disclose any medium specific for the primary Gram-negative uropathogens, and discloses no method for the determination of their presence and for simultaneously determining their antimicrobial susceptibility.

2. Claims 20-24, 26, and 31-43 Are Not Obvious Over the Inappropriate Combination of Johnson in View of Libman and Thaller

A. The Present Invention Recites the Use of a Uropathogen Specific Medium, Which Is Not Disclosed by Any Cited Art

When evaluating a claim for determining obviousness, all limitations of the claim must be evaluated. *In re Gulack,* 217 U.S.P.Q. 401 (Fed. Cir. 1983).

The claims at issue recite methods of detecting the presence of urinary pathogens in a biological sample and of simultaneously determining their susceptibility to specific antimicrobial agents. The methods of the invention require the use of a uropathogenic specific medium, i.e., a medium which allows only the growth of the primary Gram-negative urinary pathogens and allows for substantially less growth of any other bacteria of a biological matrix (defined at p. 12 of specification). The primary Gram-negative urinary pathogens are defined at p. 10 of the specification as the group of bacteria which cause at least 85-90% of the human and veterinary

urinary tract infections. This group of organisms includes, but is not limited to, *E. coli*, *Klebsiella spp.*, *Enterobacter spp.*, *Proteus mirabilis*, *Proteus vulgaris*, *Morganella morganii*, *Providencia reterri*, *Acinetobacter spp.*, and *Enterococcus faecalis* (specification, p. 8, lines 22-26).

None of the references cited by the Examiner, nor any combination thereof, disclose a uropathogen specific medium as defined in the present application. Furthermore, no motivation is found in the references to make the combination asserted by the Examiner.

B. The Cited References Disclose Simple Isolation Media and Not a Uropathogen Specific Medium as Taught by the Invention. The Cited Art Also Fails to Disclose Any Principles For Creating Such a Medium

Each of the media mentioned by Libman (MacConkey agar, EMB agar, and CLED agar, Libman, Columns 1-2) are simply standard isolation medium. It is well known in the art of microbiology that these media are for the purpose of isolation and **presumptive** identification, and that further biochemical testing is required of organisms that grow on these media in order to ascertain their identity. As the references themselves indicate, these media do not definitively determine the identity of any organism that grows on them and **do** permit the growth of contaminating organisms.

Libman states that CLED agar is "ideal in enumerating and presumptively identifying urinary flora." But Libman clearly states at Col. 4, lines 3-4 that CLED agar "supports growth of urinary pathogens **and contaminants**." Therefore, Libman discloses that the "ideal" medium (i.e., the best available) for enumerating and presumptively identifying urinary flora nevertheless allows the growth of contaminants. Libman also discloses what is already known by microbiologists -- that these media are isolation media that have the purpose of isolating colonies for further biochemical testing (Col. 3, line 64 – Col. 4, line 15). These statements of Libman

show that CLED medium, EMB agar, and MacConkey agar allow for the substantial growth of organisms other than the primary Gram-negative uropathogens because the "ideal" medium still allows for the growth of contaminants. Therefore, these media are outside the scope of the present claims, which recite a uropathogen specific medium. Such a medium is defined as a medium that allows for the growth of the primary Gram-negative uropathogens and allows substantially less growth of any other bacteria (specification, p. 12, line 11).

Furthermore, Libman states that the disclosed device "allows subculturing of bacterial colonies for further biochemical studies" (Col. 1, lines 50-52). Libman further states that a feature of the device is that it allows "easy subculturing for biochemical evaluation" (Col. 2, lines 48-53). If any medium mentioned by Libman had the selectivity the Examiner asserts, these subculturing steps would be unnecessary. And, in fact, the present invention eliminates these steps, as further explained below. For these reasons, it is shown that none of the media referred to by Libman can definitively identify uropathogens.

The media mentioned by Libman are merely isolation media that are not described by the claimed invention because they allow for the growth of contaminating organisms and will result in many false positives, as evidence below illustrates. Therefore, they are not a uropathogen specific medium as defined in the present application, and are inoperative in the present invention. The problem of contaminant growth is especially acute when testing specimens collected in the veterinary context from an unwilling animal patient. Such samples frequently are contaminated during the collection process since they must often be pipetted off of the examining room floor. In addition, obtaining samples from a urine stream is often difficult and samples often become contaminated by running along the animal patient's fur during collection. For these reasons, a uropathogen specific medium is necessary for the operation of the present

invention, and the use of isolation media suitable merely for presumptive identification will result in inaccurate results and an inoperative method.

The isolation media mentioned by Libman function according to the prior art process of identifying organisms and determining their antimicrobial susceptibility. This process generally involves four steps, which were explained by Dr. Chen in his Declaration of March, 2001 (Exhibit 1) as follows:

STEP 1: In Step 1 the sample being tested is plated out on an isolation medium (such as MacConkey agar) that allows for the growth of a limited group of organisms. The Examiner has specifically referred to MacConkey agar as an alleged example of a uropathogen specific medium (Office Action mailed 9/25/00, pp. 5-6; Office Action mailed 6/15/01, p. 3). Therefore, Dr. Chen used MacConkey agar as an illustrative example of isolation media.

As Dr. Chen explains, the purpose of Step 1 of the prior art process is the isolation of organisms for the performance of further biochemical identification tests (Declaration, March 2001, ¶ 7). Many contaminating organisms can be identified and screened out in this step based on the physical appearance of the colonies. Colonies growing on the medium that appear to be of interest are passed into Step 2. Dr. Chen explains that MacConkey agar differentiates organisms based on their ability to ferment lactose *Id.* When lactose is fermented in the medium, the fermentation process causes a drop in the pH of the medium. But not all primary Gram-negative organisms have the ability to ferment lactose. For example, *Proteus spp.* does not have this ability and will not provide a signal when growing on MacConkey agar, even though it is a primary Gram-negative uropathogen. MacConkey agar is inappropriate for use in the present invention because it will result in false positives and/or false negatives due to this reason, and for reasons further explained below.

STEP 2: Dr. Chen explains that in the second step the organisms selected by the MacConkey agar are then grown on a nonspecific medium (*Id.*, ¶ 8). The purpose of this step is to generate isolated colonies. Once these isolated colonies are grown, they are subjected to biochemical testing in Step 3 to determine the identity of the colony organisms.

STEP 3: In this step, Dr. Chen explains that the identity of the pure colonies isolated in Step 2 is determined using biochemical testing (*Id.* ¶ 9). This testing involves applying a battery of biochemical tests, which provides the biochemical information necessary to identify the colonies.

Exhibit 2 provides copies of pages from the Manual of Clinical Microbiology[1]. The passage at page 453 indicates that a number of biochemical screening tests are necessary for even "tentative" identification of Enteroacteriaceae. Table 6 of the reference lists several of those tests. Dr. Chen stated that these statements are consistent with his knowledge in the field that MacConkey agar is an isolation medium, i.e., it is useful for the isolation of bacterial colonies to be used in further biochemical analysis (*Id.* ¶ 10) and that growth on MacConkey agar does not provide any more than a mere presumptive identification of an isolated colony. Growth and signal production on MacConkey agar indicates only that the organisms are lactose fermenters. One cannot conclude that simply because a colony grows on isolation media like MacConkey agar that it is a primary Gram-negative urinary pathogen.

STEP 4: Finally, Dr. Chen explains that the purified colonies that have been definitively identified as primary Gram-negative urinary pathogens based on biochemical testing are placed in a nonselective medium containing an antimicrobial agent (*Id.* ¶ 11). If the colony fails to

[1] Manual of Clinical Microbiology, 7th edition, (ed. Murray et al.), ASM Press (Washington, DC, 1999)

grow in this medium, the organism may be susceptible to the antimicrobial agent in the living human or animal.

The linear process of isolating colonies and performing biochemical tests according to these four steps takes 3-4 days and requires the use of skilled workers. The present invention reduces these four steps (and the 3-4 day process) to ONE step that is performed within 24 hours. In the present invention, primary Gram-negative uropathogens are definitively identified and their susceptibility to antimicrobial agents is evaluated SIMULTANEOUSLY. Thus, using the present invention a user can determine in only 24 hours whether uropathogens are present and, if so, which antimicrobial agents they are susceptible to. The prior art method of using the four-step process described above requires 3-4 days of testing and the use of skilled personnel. Therefore, the present invention provides this information 2-3 days faster than the prior art methods, and reduces the four labor-intensive steps described above to a single step, which can be performed by a worker with a far lower skill level than required by prior methods.

C. MacConkey Agar Does Not Provide a Detectable Signal By Metabolism of a Signal Generating Substrate and Therefore is Not Within the Present Claims

The claims at issue recite that the presence of urinary pathogens is indicated by **"metabolism of a signal generating substrate and production of a detectable signal."** But MacConkey agar does not provide a detectable signal based on the metabolism of a signal generating substrate. Rather, in MacConkey agar the detectable signal is provided by the fermentation of lactose and a consequent drop in the pH of the medium. This drop in pH causes a dye in the medium to change color, thereby providing the detectable signal. Thus, a signal generating substrate is never metabolized in MacConkey agar, and MacConkey agar is not a medium recited for use in the present methods.

The Examiner asserted that one of ordinary skill in the art would expect success in using MacConkey agar in the present invention (Office Action mailed 9/25/00, pp. 5-6). Since the use of MacConkey agar is excluded from the present methods, this is irrelevant. Nevertheless, Dr. Chen explained in his Declaration that an isolation medium such as MacConkey agar cannot be used in the method due to the inaccuracy of the results obtained (*Id.* ¶ 10). MacConkey agar allows the growth of both lactose fermenters and non-lactose fermenters. But non-lactose fermenters do not produce a signal in MacConkey agar because the signal generation is dependent on the fermentation of lactose and a consequent drop in pH. Those primary Gram-negative uropathogens that do not ferment lactose are therefore not detectable with MacConkey agar. For example, *Proteus spp.* grows on MacConkey agar but will not produce a signal because it does not ferment lactose. Since MacConkey agar does not produce a detectable signal when *Proteus* is present, and since *Proteus* is a primary Gram-negative uropathogen, MacConkey agar (and similar isolation media) is not within the scope of these claims for this reason as well.

D. Growth on MacConkey Agar Correlates Poorly With Established Methods of Identifying Organisms. MacConkey Agar is Not a Uropathogen Specific Medium As Defined in the Application

In order to demonstrate in the laboratory that MacConkey agar and other isolation media of the prior art are inoperative in the present invention, Dr. Chen designed and performed an experiment to investigate the performance of MacConkey agar (modified as the Examiner, but not the prior art, suggested) applied in the present invention. These results were reported in his Declaration filed November 13, 2001.

None of the cited references discloses or suggests the addition of a signal substrate to MacConkey agar. The prior art discloses no advantage to be gained from such a step and such action serves no apparent purpose, other than to attempt to (unsuccessfully and impermissibly) reconstruct the present invention from various art references using the present claims as a blueprint. Therefore no motivation is provided by the art or by the knowledge of one of ordinary skill in the art to combine a signal substrate with MacConkey agar. But the Examiner maintained that this was an obvious modification to make (Office Action mailed 6/15/2001, p. 4). Therefore, to irrefutably demonstrate the inoperability of isolation media in the present invention, Dr. Chen took the extraordinary step of adding a signal substrate to MacConkey agar in order to demonstrate the poor selective power of isolation media, and that these isolation media are not uropathogen specific media as defined in the present application and recited in the claims.

As reported in his Declaration, a first assay set included a well containing a uropathogen specific medium of the invention, and a second assay set included MacConkey agar with the addition of 4-Mu phosphate as a substrate. 97 different feline and canine urine samples were collected and analyzed. The results were compared to the Traditional Microbiological Culture and Susceptibility Assay (TMCSA), which is accepted in the art as a "gold standard." (Declaration, pp. 2-3). The TMCSA is based on the four-step prior art process described above.

Twenty-three of the urine samples were found to be positive for the primary Gram-negative uropathogens according to TMCSA. As the Table on p. 4 of the Declaration (and reproduced below) illustrates, the method of the present invention (using a uropathogen specific medium) was able to detect all 23 positive samples. But the MacConkey agar was able to detect only 14 of the 23 positive samples. Thus, MacConkey agar was able to identify only about 60%

of the samples containing UTI organisms. Of those 14, three samples were reported to have a very weak signal, and an additional 9 samples provided a weak signal. Therefore, the actual ability of MacConkey to identify Gram-negative uropathogens is no greater than 60%, and indeed may be much lower, depending on interpretation of the results.

Table 1

	Gram (-)	Ciprofloxacin		Amoxicillin	
	Uropathogen	Resistant	Susceptible	Resistant	Susceptible
TMCSA[2]	23	0	23	13	10
Uropathogen Base[3]	23	1	22	13	10
MacConkey Base[4]	14[5]	1	13	8[6]	6

Using TMCSA, all 23 samples were shown to be susceptible to ciprofloxacin. But the method using MacConkey agar correctly identified only 13 of the 23 ciprofloxicin susceptible samples. Using the presently claimed method (with a uropathogen specific medium) 22 of the 23 susceptible samples were correctly identified. Thus, the method using MacConkey agar correctly predicted ciprofloxacin susceptibility in only 56% of cases, while the presently claimed methods correctly identified over 95% of cases.

Finally, 10 samples were shown by TMCSA to be resistant to amoxicillin. The present invention correctly identified amoxicillin susceptibility in 100% of cases, while the MacConkey medium correctly identified only 60%.

[2] TMCSA: Traditional microbiological culture and susceptibility assay.

[3] Uropathogen specific medium.

[4] MacConkey base medium with the addition of 4-Mu phosphate enzyme substrate.

[5] Among these 14 positive samples, 9 exhibited weak fluorescent signal and 3 showed very weak fluorescent signal.

[6] Among these 8 samples, 4 exhibited weak fluorescent signal and 4 showed very weak signal.

In view of these results, it is apparent that MacConkey agar is inoperable in the present invention and is not a medium that "allows only the growth of the primary Gram-negative uropathogens," as defined and claimed in the present case (specification, p. 12, lines 11-14). No cited reference discloses, suggests, or enables the person of ordinary skill to make a uropathogen specific medium as claimed and defined in the application. Furthermore, no motivation is provided to combine any references to arrive at a method of determining the presence of the primary Gram-negative uropathogens, and simultaneously determine their antimicrobial susceptibility, as presently claimed.

E. Other Isolation Media of the Prior Art Are Also Inoperable and Non-Enabling in the Invention And Are Also Not Uropathogen Specific Medium As Defined in the Application

In addition to MacConkey agar, Libman mentions other prior art media including EMB Agar and CLED agar (Col 3, line 64 – Col. 4, line 15). Libman describes MacConkey agar as "preferred in the presumptive identification of pathogens" and discloses the use of two separate media (e.g., MacConkey agar and CLED agar) in the presumptive identification of pathogens (Col. 3, lines 64-66). Thus, Libman indicates that MacConkey agar, CLED agar, or EMB agar, by themselves, are inadequate for even presumptive identification since two distinct media are used to achieve only presumptive identification in one culturing (Col. 3, lines 64-67). Thus, none of these media have the selective power necessary to be a uropathogen specific medium as defined in the application.

Libman also states that organisms growing on CLED agar are identified by physical characteristics, such as the color of colonies and media and/or morphology (Col. 4, line 7). Thus, there is no metabolism of a signal generating substrate and production of a detectable

signal, as recited in the present claims, nor any motivation to add a signal generating substrate to CLED agar. Therefore CLED agar is also excluded from the present claims. Thus, Libman does not disclose the presently claimed methods, nor does Libman disclose a medium necessary to practice the methods.

The Examiner also includes the T-mod medium of Thaller in the rejection. But T-mod is another prior art medium for isolation and presumptive identification of Enterbacteriaceae, as stated by Thaller herself ("The present investigation was undertaken to evaluate a new medium (T-mod) for isolating and presumptively identifying members of the *Enterobacteriaceae* which commonly cause urinary tract infections," Thaller, p. 791, left column, lines 7-9). Thaller discloses identifying organisms by isolation on T-mod and a variety of biochemical tests, and not by their ability to grow on the medium and provide a signal when a signal generating substrate is metabolized, as in the present invention. At p. 791, right column, paragraph 1 of Thaller, the identification of organisms is disclosed based on 1) the color of the colony growing on the medium; 2) fluorescence of a beta-glucuronidase substrate around the colony; and 3) the results of cytochrome oxidase and indole with oxidase sticks and filter paper saturated with Kovacs reagent.

Thaller also states that the colony counts and sizes of tested Gram-negative strains showed no significant differences on T-mod and MacConkey media (p. 791, right column). Therefore, T-mod medium, like MacConkey agar, is unsuitable for use in the present methods for reasons described above with respect to MacConkey agar. Thaller does not disclose a medium with a selective power necessary to be a uropathogen specific medium, nor does Thaller disclose any principles for creating such a medium. Therefore the medium of Thaller (like MacConkey agar) is an alternative medium for isolation and presumptive identification. Thaller

does not disclose a uropathogen specific medium of the presently claimed methods, where metabolism of a signal generating substrate and production of a detectable signal indicates the presence of uropathogens. Since Thaller depends on performing biochemical testing on a pure colony, it is clear that T-mod medium does not have the selective power to operate in the invention. Rather, it is another isolation medium that is inappropriate and inoperative in the claimed invention, which recites identification of organisms based on their ability to metabolize a signal generating substrate and provide a detectable signal. Thaller does not disclose any methods for detecting the presence of urinary pathogens and the simultaneous determination of their susceptibility to antimicrobial agents.

As a matter of law, if each and every element of the claimed invention is not taught or suggested by the prior art, a prima facie case of obviousness has not been established. *In re Royka,* 490 F.2d 981, *985;* 180 U.S.P.Q. 580 (C.C.P.A. 1974); MPEP § 2142. For the reasons stated, a prima facie case for obviousness has not and cannot be established using the combination of references cited by the Examiner and relief from the rejection is requested.

F. The Inappropriate Combination of Johnson in view of Libman and Thaller, and further in view of Odaka Does Not Support a Prima Facie Case of Obviousness

Claims 38-42 are similar to the previous claims except that they recite the inclusion of yeast extract in the uropathogen specific medium. The Examiner states that Odaka teaches a culture medium to enhance the growth and rapid detection of *E. coli* (a known uropathogen) and specifically teaches that methyl-umbelliferyl substrates can be detected in a medium comprising yeast extract (Office Action mailed 1/3/03, p.5).

However, with or without the recitation of yeast extract, the addition of Odaka to the combination fails to provide a prima facie case of obviousness, for reasons already explained

above. The medium contains peptone, sodium chloride, yeast extract, glycerol, dipotassium hydrogen phosphate, sodium pyruvate, potassium nitrate, and bile agar. Odaka completely fails to disclose any uropathogen specific medium recited in the claimed methods or to teach any principles for creating such a medium. The Applicants do not claim to have invented the addition of yeast extract to any microbiological media, nor the addition of methyl-umbelliferyl substrates to any media. The Applicants claim to have invented a method for the determination of the presence of the primary Gram-negative uropathogens in biological samples and the simultaneous determination of their antimicrobial susceptibility. Odaka does not disclose such a method, nor a medium necessary to conduct such a method. Simply adding Odaka's disclosure of a growth and multiplication medium for Colibacillus does not cure the deficiencies described above.

G. The Inappropriate Combination of Johnson in view of Libman and Thaller and further in view of Brocco Also Fails to Support a Prima Facie Case of Obviousness

The combination of Johnson in view of Libman and Thaller has been discussed above. Claims 26 and 37 specify the antimicrobial agents that are used in one embodiment of the invention. Adding Brocco to the combination does not cure the failure of the rejection to achieve a prima facie case of obviousness.

The Examiner finds that "Brocco teaches a method of determining susceptibility of uropathogens, to amoxicillin and a clavulanic acid mixture." But as previously pointed out by the Applicants (Response mailed June 3, 1999, p. 5; Response mailed 2/8/98, p. 12) Brocco in no way assists in providing a prima facie case of obviousness since it also fails to disclose the presently claimed methods, or a uropathogen specific medium recited in the methods. In fact,

Brocco does not disclose a medium specific for ANY organism. Nor is any motivation provided by the prior art to combine Brocco with Libman and Thaller. According to Brocco, the organisms must necessarily be pre-grown and added to the test medium as pure cultures. This is apparent from reading Example 1 (p. 4, line 32 et seq.; also see p. 4, lines 3-11 directing the use of sterile containers) of Brocco, which directs the user to transfer "10 ul of Gram-negative bacteria" and "200 ul of gram positive bacteria." (p. *5,* lines 14-15) which can be obtained only by pre-growing them. The samples are then incubated with these pre-grown, pure cultures and the results determined.

Conversely, in the present invention the user collects a sample of urine from (for example) an animal patient. The sample is likely to be contaminated with environmental bacteria because the urine is collected using a non-sterile technique. The collection technique often results in the sample running along the animal's fur and being contaminated with environmental bacteria before being placed into the medium. In the present methods, it does not matter that a sample is not sterile because the medium used is uropathogen specific, i.e., allows only for the growth of the primary Gram-negative urinary pathogens (pp. 10 and 12 of specification define these terms). Thus, contaminating bacteria that are not primary Gram-negative urinary pathogens will not affect the method because they cannot grow in the medium recited by the method. Therefore, adding the nonselective medium of Brocco to the rejection does not cure the deficiencies noted above and the claimed methods are not obvious over Libman and Thaller in view of Brocco.

H. The Inappropriate Combination of Libman, Thaller, and Odaka, and Further in View of Brocco Also Fails to Support a Prima Facie Case of Obviousness

Johnson in view of Libman, Thaller, and Odaka is discussed above. Brocco is also discussed above. Claim 43 recites specific antimicrobial agents that are used in one embodiment of the invention. Adding Brocco to the combination does not cure the deficiencies already discussed above, since Brocco also does not disclose the claimed methods, nor a uropathogen specific medium recited in the methods and defined in the specification (p. 12, lines 11-14). Nor is any motivation provided by the prior art to make the asserted combination.

3. The Examiner Has Used Impermissible Hindsight in Making an Erroneous Determination of Obviousness

As a matter of law, if each and every element of the claimed invention is not taught or suggested by the prior art, *a prima facie* case of obviousness has not been established. *In re Royka,* 490 F.2d 981, *985;* 180 U.S.P.Q. 580 (C.C.P.A. 1974); MPEP § 2142. A proper analysis under § 103 requires consideration of whether the prior art would have suggested to one of ordinary skill in the art to carry out the claimed process. One must also consider whether the prior art would have revealed that one of ordinary skill in the art would have had a reasonable expectation of success in doing so. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure. *Id.*

In the present case the prior art does not disclose any method for the determination of the presence of the primary Gram-negative uropathogens and the simultaneous determination of their antimicrobial susceptibility. In fact, the references do not even suggest it might be possible to make these two determinations simultaneously and without resorting to the laborious procedures of the prior art. Furthermore, the prior art does not disclose what ingredients must be

combined or what principles to follow in order to arrive at a uropathogen specific medium (i.e., a medium which allows for the growth of the primary Gram-negative urinary pathogens, and for substantially less growth of any other bacteria) (see definition, p. 12, lines 11-14 of the specification). Indeed the prior art does not even disclose that such a medium is possible to obtain. The present application specifically teaches such methods and a medium necessary to conduct the methods at page 19 of the specification.

These concepts are taught only by the present application. Therefore, it appears the Examiner has attempted (unsuccessfully) to reconstruct the invention by making selections from the prior art using Applicant's own disclosure as a blueprint. But the law does not allow an obviousness determination to be based on hindsight where that which only the inventor taught is used against its teacher. *W.L. Gore Assoc. Inc., v. Garlock, Inc.,* 721 F.2d 1540, 1553 (Fed. Cir. 1983). The Federal Circuit has clearly stated that it is erroneous to use the Applicant's disclosure as a blueprint and to thereby reconstruct the claimed invention from the prior art.

> It is error to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a "blueprint." When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself. It is critical to understand the particular results achieved by the new combination. *Interconnect Planning Corp. v. Feil*, 227 USPQ 543 (Fed. Cir. 1985).

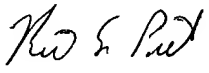
Nevertheless, even making such selections does not allow one to arrive at the present invention because all of the claimed elements are not present in the art, i.e., no reference teaches a uropathogen specific medium. Furthermore, no motivation is found in the art to make the combinations that the Examiner has made. The motivation comes only from reviewing the Applicant's claim and seeking to assemble the invention from the prior art. Even so, the combination fails to provide the claimed invention since it does not exist in any of the cited references, nor even in their inappropriate combination.

For the foregoing reasons, a prima facie case of obviousness is not established over the references cited by the Examiner and relief from the rejection is sought.

CONCLUSION

In view of the above discussion, Applicant submits that claims 20-24, 26, and 31-43 are allowable. Applicant respectfully requests that they be allowed and passed to issue.

Respectfully submitted,



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APPENDIX A

20. A method of detecting the presence of urinary pathogens in a biological sample and of simultaneously determining the susceptibility of the urinary pathogens to antimicrobial agents, said method comprising:

providing a multicompartment assay device comprising:

at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; at least one compartment comprising a uropathogenic specific medium; and, at least one compartment comprising an antimicrobial susceptibility interpretation medium;

placing a portion of the biological sample respectively in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; said at least one compartment comprising a uropathogenic specific medium; and, said at least one compartment comprising an antimicrobial susceptibility interpretation medium comprising an antimicrobial agent;

whereby metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms indicates the presence of microbial organisms in the sample; metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising a uropathogenic specific medium indicates the presence of urinary pathogens in the sample; and metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising an antimicrobial susceptibility interpretation medium indicates that the organisms lack susceptibility to the antimicrobial agent comprised in said antimicrobial susceptibility interpretation medium; and

examining the compartments to determine the presence of urinary pathogens in said biological sample and the susceptibility of said urinary pathogens to said antimicrobial agents.

21. The method of claim 20, wherein the biological fluid is urine.

22. The method of claim 21, wherein the urinary pathogens are primary Gram-negative urinary pathogens.

23. The method of claim 22 wherein the primary Gram-negative urinary pathogens comprise *Enterobacteriacae*.

24. The method of claim 22 wherein the primary Gram-negative urinary pathogens are selected from the group consisting of: *Escherichia coli, Klebsiella spp., Enterobacter spp., Proteus mirabilis, Proteus vulgaris, Morganella morganii, Providencia retteri*, and *Acinetobacter spp.*

26. The method of claim 20 wherein the at least one antimicrobial susceptibility interpretation medium comprises amoxicillin, clavulanic acid/amoxicillin, or enrofloxacin.

31. The method of claim 20 wherein the signal generating substrate is fluorogenic or chromogenic.

32. (New) A method of detecting the presence of urinary pathogens in a biological sample and of simultaneously determining the susceptibility of the urinary pathogens to antimicrobial agents, said method comprising:

providing a multicompartment assay device comprising:

at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; at least one compartment comprising a uropathogenic specific medium comprising a methyl-umbelliferyl substrate; and, at least one compartment comprising an antimicrobial susceptibility interpretation medium;

placing a portion of the biological sample respectively in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; said at least one compartment comprising a uropathogenic specific medium comprising a methyl-umbelliferyl substrate; and, said at least one compartment comprising an antimicrobial susceptibility interpretation medium comprising an antimicrobial agent;

whereby metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms indicates the presence of microbial organisms in the sample;

metabolism of a methyl-umbelliferyl signal generating substrate and production of a detectable signal in said at least one compartment comprising a uropathogenic specific medium indicates the presence of urinary pathogens in the sample; and metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising an antimicrobial susceptibility interpretation medium indicates that the organisms lack susceptibility to the antimicrobial agent comprised in said antimicrobial susceptibility interpretation medium; and

examining the compartments to determine the presence of urinary pathogens in said biological sample and the susceptibility of said urinary pathogens to said antimicrobial agents.

33. (New) The method of claim 32, wherein the biological fluid is urine.

34. (New) The method of claim 33, wherein the urinary pathogens are primary Gram-negative urinary pathogens.

35. (New) The method of claim 34 wherein the primary Gram-negative urinary pathogens comprise *Enterobacteriacae*.

36. (New) The method of claim 34 wherein the primary Gram-negative urinary pathogens are selected from the group consisting of: *Escherichia coli, Klebsiella spp., Enterobacter spp., Proteus mirabilis, Proteus vulgaris, Morganella morganii, Providencia retteri*, and *Acinetobacter spp*.

37. (New) The method of claim 32 wherein the at least one antimicrobial susceptibility interpretation medium comprises amoxicillin, clavulanic acid/amoxicillin, or enrofloxacin.

38. (New) A method of detecting the presence of urinary pathogens in a biological sample and of simultaneously determining the susceptibility of the urinary pathogens to antimicrobial agents, said method comprising:

providing a multicompartment assay device comprising:

at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; at least one compartment comprising a uropathogenic specific medium comprising yeast extract; and, at least one compartment comprising an antimicrobial susceptibility interpretation medium;

placing a portion of the biological sample respectively in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms; said at least one compartment comprising a uropathogenic specific medium comprising yeast extract; and, said at least one compartment comprising an antimicrobial susceptibility interpretation medium comprising an antimicrobial agent;

whereby metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising a medium capable of sustaining growth of total microbial organisms indicates the presence of microbial organisms in the sample; metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising a uropathogenic specific medium comprising yeast extract indicates the presence of urinary pathogens in the sample; and metabolism of a signal generating substrate and production of a detectable signal in said at least one compartment comprising an antimicrobial susceptibility interpretation medium indicates that the organisms lack susceptibility to the antimicrobial agent comprised in said antimicrobial susceptibility interpretation medium; and

examining the compartments to determine the presence of urinary pathogens in said biological sample and the susceptibility of said urinary pathogens to said antimicrobial agents.

39. (New) The method of claim 38, wherein the biological fluid is urine.

40. (New) The method of claim 39, wherein the urinary pathogens are primary Gram-negative urinary pathogens.

41. (New) The method of claim 40 wherein the primary Gram-negative urinary pathogens comprise *Enterobacteriacae.*

42. (New) The method of claim 40 wherein the primary Gram-negative urinary pathogens are selected from the group consisting of: *Escherichia coli, Klebsiella spp., Enterobacter spp., Proteus mirabilis, Proteus vulgaris, Morganella morganii, Providencia retteri*, and *Acinetobacter spp.*

43. (New) The method of claim 38 wherein the at least one antimicrobial susceptibility interpretation medium comprises amoxicillin, clavulanic acid/amoxicillin, or enrofloxacin.